Revised

Comments on

Draft Report on Carcinogens
Background Document for

Diesel Exhaust Particulates

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GENERAL COMMENTS ON CLASSIFICATION OF DIESEL PARTICULATES WITH RESPECT TO HUMAN CARCINOGENICITY

1. The document presents information, but does little to synthesize the information in each chapter into a conclusive summary.

For the most part, the draft document summarizes the existing information reasonably, although some important issues are not addressed. The document would be a more useful summary if a concluding synthesis was added to the end of each chapter. The reader is left "hanging" at the end of the chapters without being presented with a summary of the key conclusions that can be drawn from the foregoing information regarding the likely human carcinogenic potential of diesel particulate. In some cases, the lack of summary can leave the reader with a misimpression. For example, the experimental carcinogenesis chapter ends with a description of the use of mouse skin painting results for comparative risk assessment, rather than a summary of the utility of animal data for judging human cancer potential. Risk assessment approaches using other animal and human data are not discussed; thus, the impression is left that the approach described is recommended.

2. The document does not adequately portray the issue of changing diesel emissions

Diesel engine and fuel technologies have changed considerably during the past 10 years, and even more strikingly over the longer period during which the toxicological and epidemiological studies were done. Changes in engines and fuels have reduced emissions of soot and nitrogen oxides. There is a current research emphasis and ongoing debate on the extent to which organic compounds formerly adsorbed to elemental carbon to form soot are now emitted as ultrafine particles of organic condensate. Examples of citations framing this issue are: Bagley et al., Characterization of Fuel and Aftertreatment Device Effects on Diesel Emissions, Health Effects Institute Research Report No. 76, 1996; and Baumgard and Johnson, The Effect of Fuel and Engine Design on Diesel Exhaust Particle Size Distributions, Society of Automotive Engineers (SAE) technical paper No. 960131, 1996. The shifts in the nature of diesel emissions and their potential health implications are not resolved.

Although the long useful life of diesel engines can be invoked to justify interest in the toxicity of past emissions, the issue of present concern is the potential for future human health risks. Our existing health information was derived from epidemiological and toxicological studies conducted largely over the past 25 years. There are not even any animal studies of emissions from current technology engines and fuels, much less epidemiological studies which, of course, could not yet have been conducted.

While the impact of changing emissions is uncertain, there are data suggesting that risks are likely to be lessened by the changes. It was shown, for example, that reducing the sulfur, aromatic, and polycyclic aromatic hydrocarbon contents of diesel fuel, as has been done in California, substantially reduce the emission of particulate and mutagenic agents,

and correspondingly reduce the amounts of mutagenic activity emitted by the same engine under the same conditions of use (Norbeck and Smith, Evaluation of Factors that Affect Diesel Exhaust Toxicity, Final Report, Contract 94-312, University of California, Riverside [aka "CE-CERT" Report]).

The first chapter should acknowledge this problematic issue. It is not reasonable to expect the chapter to deal with the issue in detail, but it is neither is it reasonable for the chapter to ignore the issue. Even if we understood past diesel-related health risks perfectly, which we don't, it is not known how changes in emissions might cause future health risks to differ from past risks. The importance of the issue to this report is its implication for the degree of certainty with which the carcinogenicity of diesel particulate can be judged at this time.

3. **The chapters on experimental carcinogenesis and genotoxicity present an incomplete view.**

Our current information from animals indicates that a concern for human cancer risk from high level exposures to diesel soot is plausible, but neither confirms that risk nor provides dependable quantitative estimates of that risk. Results from animals continue to demonstrate that extracts of diesel soot have genotoxic potential and are carcinogenic in biological assays if applied in high concentrations, as has been known from the 1950s (Kotin et al., Aromatic Hydrocarbons III: Presence in the Particulate Phase of Diesel Engine Exhausts and the Carcinogenicity of Exhaust Extracts, Arch. Ind. Health 11:113-120, 1955). The only consistent lung tumorigenesis in animals is in rats, and it has been proven repeatedly that the carcinogenicity of diesel exhaust in other rodents can not be predicted from the rat response.

As chapter 4 appropriately notes, but does not describe thoroughly, the rat lung response is poorly-specific for the chemical nature of the particles, as long as the particles are respirable, poorly-soluble, and administered at levels that overwhelm lung clearance. This problem has been recognized by a number of working groups over the past 10 years. The widespread and growing consensus regarding the peculiarity of the rat response to high-level particle exposures was most recently reflected by the report of the March 1998 Workshop on the Relevance of the Rat Lung Response to Inhaled Particulates in Human Risk Assessment, sponsored by the Risk Sciences Institute of the International Life Sciences Institute (in press). There is substantial and continually growing evidence that the rat response to chronic, extremely high-level exposures to particles is not predictive for human lung cancer risk, and is of questionable use for predicting hazard. This is especially true for risks from much lesser exposures.

The aggregate data indicate that the rat lung response to diesel soot has a threshold, which should be mentioned in the document. The importance of this issue lies in the use of the rat lung as a biological test system to support the carcinogenicity of diesel particulate. Even if the rat response cannot be directly extrapolated to the human, it could be viewed as an assay with at least the relevance of an assay like mouse skin

painting. From this perspective, the dose-response of this assay becomes important. The threshold for rat lung carcinogenesis appears to occur at an exposure level where there are concurrent thresholds for persistent inflammation, fibrosis, and other progressive tissue changes. As summarized in Mauderly, Diesel Exhaust, in Environmental Toxicants: Human Exposures and their Health Effects, Lippmann, Ed., Wiley (in press), results from over 1300 rats in eight studies from five laboratories in four countries show no response below a weekly exposure of 106 mg hr m^{-3}. This exposure would represent a continuous 24 hr average exposure to 630 $\mu g/m^3$, and a 40 hr exposure to 2650 $\mu g/m^3$. The response threshold was tested statistically by Valberg, who demonstrated its existence and derived an upper 95% confidence level positive slope for the aggregate data which yielded two tenths of one percent increase above the control tumor incidence at a lifetime continuous exposure of 500 $\mu g/m^3$ (Dr. Peter Valberg, presentation at May 1998 meeting of the Clean Air Scientific Advisory Committee).

Chapter 5 correctly points out that diesel soot extracts given at high doses are genotoxic and carcinogenic in non-inhalation assays. The document does not, however, frame this finding in the context of the relative tissue doses that occur in the assays vs. those likely to occur in exposed humans. The important difference of several orders of magnitude larger dose over considerably shorter times in the bioassays should at least be mentioned.

The draft report correctly states that lung DNA adduct levels are increased in rats exposed to high concentrations of diesel particulate. The report does not, however, qualify the association by noting that the adduct levels are not increased progressively during chronic exposure and the adduct response is also induced by identical exposure to organic-poor carbon black. The key report by Randerath et al. (Pulmonary Toxicity of Inhaled Diesel Exhaust and Carbon Black in Chronically Exposed Rats, Part II: DNA Damage, Health effects Institute Research Report No. 68, 1995) was not cited. The increases of adducts measured to date are mostly, if not entirely, due to increases in adducts that are normally present. It is not yet clear whether or not diesel-specific adducts are induced.

4. **If a choice must be made between the two classifications under consideration, our present information much more strongly supports a classification that diesel exhaust particulate is reasonably anticipated to be a human carcinogen.**

Present information indicates that it is plausible that diesel soot, inhaled at some high concentration and for some prolonged time has in the past contributed to human lung cancer risk among certain groups of workers. The plausibility is based on the known genotoxicity of some soot constituents and the weight of evidence for an association between occupations involving inhalation of diesel emissions and a small increase in past cancer incidences. Unfortunately, lack of exposure data prevents us from definitively confirming or accurately determining the exposure-response relationship of the response from existing data, no matter how we might manipulate them.

Several uncertainties prevent the conclusion that diesel soot is presently a "known" human carcinogen, on any basis except personal views of the weight of evidence. First, we have neither epidemiological nor toxicological data on emissions from current (or future) generation engines and fuels. Our judgement is retrospective and the nature of the material under debate is changing. Second, while biological systems can clearly demonstrate the genotoxicity of high tissue doses of soot extracts, we have yet only a very modest ability to relate that genotoxic potential to target tissue doses in humans under realistic exposure scenarios. Third, we do not yet have an adequate demonstration of material-specific lung cancer induction in animals. Current evidence discounts use of the rat response, and we do not have adequate information from other species upon which to base a positive conclusion. Fourth, we can have only very modest confidence in our estimates of past exposures of occupational groups to diesel soot and potentially confounding agents or influences. The various current estimates may or may not be adequately accurate, but that can never be known.

In conclusion, the status of our present information does not assure that diesel exhaust particulate is not a human carcinogen, but neither does not provide a sound basis for declaring that the material, as it exists today, is a known human carcinogen. A classification of "reasonably anticipated" might be supported by the aggregate current information. However, the incongruity between the term "anticipated" with the fact that our information is from studies of increasingly outdated emissions should be fully acknowledged.

ADDITIONAL SPECIFIC COMMENTS ON DRAFT BACKGROUND DOCUMENT

Chapter 3

In two places on pages 34 and 35, the statement is made that misclassification may provide an explanation for the small size of the calculated relative risks. This statement suggests a bias that the actual risk must be higher. The basis for this bias is not clear.

Chapter 4

Page 37, para. 3: The Nikula et al. 1995 reference is wrong. Nikula et al. did not conduct exposures of rats to filtered exhaust. In addition to the Brightwell group, the Heinrich group conducted exposures to filtered exhaust. This was done in two studies, the first published in 1986 and the second published in 1995.

Page 37, para 3: The skepticism about the predictive value of rat lung tumor data for human cancer risk is based on a lack of confirmed risk in humans from carbon black. While this is not untrue, the much greater basis for skepticism is the similar response of the rat to a wide range of respirable, poorly-soluble particles. It appears at this point that the rat is likely to respond with lung tumors to most any poorly-soluble respirable particle if given in sufficient concentration for

sufficient time. The fact that the rat, but not the human, manifests a largely nonspecific lung tumor response to chronic loading of the lung with dusts is a convincing basis for lack of applicability.

Page 45, para 2: The concentrations of soot in lungs of mice in the Mauderly et al. study are more properly compared to those in rats from the same study, not the rats from the Nikula et al. study. The rat and mice lung burdens were compared in Henderson, et al., Fundam. Appl. Toxicol. 11: 546-567, 1988. The lung burdens were indeed similar on a size-adjusted basis. The concept presented is not wrong, but the comparative rat data are more properly those from the earlier report.

Page 46, Section 4.3.2: The point that concentrated extracts of diesel soot can cause skin tumors in mice is true, as has been known since the 1950s. This section appears odd in the chapter, because it focuses not on the skin response and its relevance to inhalation, but on the estimation of human lung cancer risk using the skin data. The preceding sections of the chapter did not describe the many different estimates that have been generated from the animal data. It is not clear why that approach was taken in this section. The result is that the reader is left with an impression that, among all the animal data, the skin tumor response somehow makes a case, or perhaps the best case, for human risk from diesel exhaust. Much more support would be needed to make such a case.

Chapter 5

Page 49, Heading of Section 5.3.1: This heading is misleading, because the section describes DNA adduct levels in respiratory tract tissues, not lymphocytes. There is no information indicating that the increases in adduct levels in the tissues were due to adducts in lymphocytes, nor was such a statement made in the text.

Page 49, para. 4: First, the Gallagher et al. 1990 citation is either incorrect, or it is missing from the reference list. Second, it seems odd that the document would showcase a study involving a total of only 5 mice spread over three dose levels.

Pages 49-50, Section 5.3.1. This section fails to cite the most extensive evaluation of DNA adducts in the respiratory tracts of rats exposed chronically to diesel exhaust. The work by Randerath et al. (cited above) is of interest for three reasons. First, it demonstrated similar adduct responses to diesel exhaust and carbon black. Second it demonstrated no progression in adduct levels during chronic exposure. Third, it showed, as other studies have, that the increases in adduct levels occur in adducts that also occur in controls. While the inclusion of this citation does not alter the correct conclusion that DNA adduct levels are increased in rodents exposed to diesel exhaust, its exclusion is inappropriate.

THE DOCUMENT DOES NOT ADEQUATELY PORTRAY THE ISSUE OF CHANGING EMISSIONS

- The categories "known" and "anticipated" should focus on present and future risks, not on past risks
- Changes in diesel engines and fuels have resulted in changes in emissions
- Some of the changes would reduce cancer risk
- The health implications of other changes can not yet be estimated

CE-CERT STUDY RESULTS

(Cummins L-10-310, Hot Start, Heavy-Duty Cycle)

		Fuels		
Emissions		**Pre-'93**	**Reformulated**	**Low Aromatic**
PAH (27)	mg/Bhp-hr	1.56	0.98 (-37)	0.75 (-52)
NitroPAH (5)	µg/Bhp-hr	4.85	4.40 (-9)	4.04 (-17)
Mutagenicity	Rev/Bhp-hrx10^6	7.4	4.7 (-36)	3.8 (-49)

THE CHAPTERS ON EXPERIMENTAL CARCINOGENESIS AND GENOTOXICITY PRESENT AN INCOMPLETE VIEW

- Information on the likely utility of the rat lung tumor results needs strengthening
- Information on DNA adducts needs strengthening

  Comparative dosimetry is not portrayed

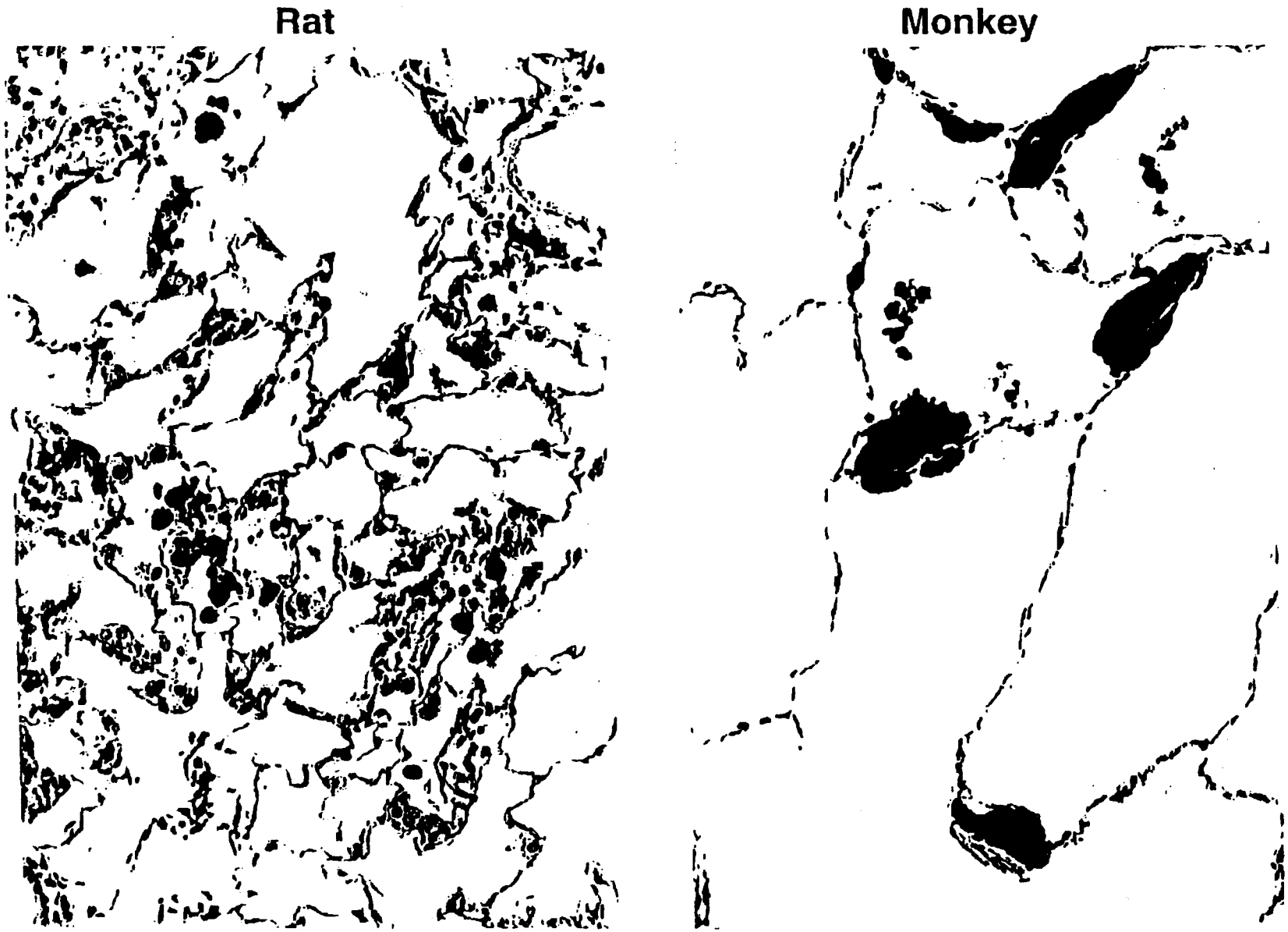
  Rat adduct information is incomplete

    Increases are not increase progressively

    Increases are due to "normal" adducts

    Increases in diesel-specific adducts not clear

RESPONSE TO CHRONIC INHALATION OF DIESEL SOOT



SOOT EXTRACT DOSES: MICE VS. MEN

- Worker Exposed 30 yrs @ 1000 µg/m^3

  20 LPM x 40 hr/wk x 50 wk/yr
  70 kg, 20% deposition, 30% extractable
  100% bioavailable

  62 mg extract/kg spread over 30 yrs
  <u>6 µg/kg/day</u>

- Mouse skin painting (Gallagher et al.)

  30 g mice painted with 20-120 mg

  667 – 4000 mg extract/kg over 54 days
  <u>12,352 – 74, 075 µg/kg/day</u>

OF THE TWO CLASSIFICATIONS UNDER CONSIDERATION, "REASONABLY ANTICIPATED" IS MORE STRONGLY SUPPORTED

- No amount of maniuplation will draw a more definitve conclusion from past epidemiological data - exposures simply aren't known
- We have very modest ability to extrapolate critical cellular doses from assays with soot extracts to human doses
- Both "known" and "anticipated" are incongruous with the fact that our present knowledge is from progressively outdated emissions